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Blood Pressure Control in Conventional Hemodialysis.

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Abstract

Hypertension among patients on hemodialysis is common, difficult to diagnose and often inadequately controlled. Although specific blood pressure (BP) targets in this particular population are not yet established, meta-analyses of randomized trials showed that deliberate BP-lowering with antihypertensive drugs improves clinical outcomes in hemodialysis patients. BP-lowering in these individuals should initially utilize non-pharmacological strategies aiming to control sodium and volume overload. Accordingly, restricting dietary sodium intake, eliminating intradialytic sodium gain via individualized dialysate sodium prescription, optimally assessing and managing dry-weight and providing a sufficient duration of dialysis are first-line treatment considerations to control BP. If BP remains uncontrolled despite the adequate management of volume, antihypertensive therapy is the next consideration. Contrary to non-hemodialysis populations, emerging clinical-trial evidence suggests that among those on hemodialysis, β-blockers are more effective than agents blocking the renin-angiotensin-system (RAS) in reducing BP levels and protecting from serious adverse cardiovascular complications. Accordingly, β-blockade is our first-line approach in pharmacotherapy of hypertension. Long-acting calcium-channel-blockers and RAS-blockers are our next considerations, taking into account the co-morbidities and the overall risk profile of each individual patient. Additional research efforts, mainly randomized trials, are clearly warranted in order to elucidate aspects of management that remain elusive in hypertensive dialysis patients.

Keywords

BP control; hypertension; hemodialysis; ESRD; treatment

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INTRODUCTION

Hypertension is a very common clinical condition among patients on hemodialysis and is often inadequately diagnosed and poorly controlled (1;2). The inverse or U-shaped association of pre- and postdialysis blood pressure (BP) with mortality raised concerns on whether hypertension among hemodialysis patients is harmful (3–5). However, elevated BP assessed with home BP recordings or with interdialytic ambulatory BP monitoring (ABPM) provides a direct and clear mortality signal (3;6–8). Additional support to this notion is provided by prospective studies associating elevated office BP recorded outside of dialysis with excess risk for cardiovascular events and all-cause mortality (9;10).

Although the exact levels at which BP should be targeted remain elusive (11), meta-analyses of randomized trials showed that BP-lowering with the use of antihypertensive therapy improves clinical outcomes (12;13), particularly if patients are hypertensive (12). A recent trial randomizing hemodialysis patients to lower versus higher predialysis BP targets suggested that intensive BP-lowering in conventional hemodialysis is feasible and does not exacerbate the risk of serious adverse events (14). Hypertension should managed first by non-pharmacological strategies aiming to control sodium and volume overload. If BP remains unresponsive to volume management strategies, initiation of antihypertensive therapy is the next treatment consideration (15).

In this article, we provide an overview of “what we know” and what remains to be elucidated in the field of BP control in conventional hemodialysis. The focus of this article is on pharmacological management of hypertension in the era of evidence provided mainly from randomized trials.

NON-PHARMACOLOGICAL MANAGEMENT

Adequate management of sodium and volume excess are the first treatment considerations for controlling BP in conventional hemodialysis (16). Dietary sodium intake is recommended not to exceed 2 g daily (corresponding to 5 g of salt intake) as an approach to decrease the sense of thirst, limit interdialytic weight gain (IDWG) and aid the feasibility of dry-weight probing (17). Individualized prescription of dialysate sodium according to the predialysis plasma sodium concentration is another therapeutic intervention aiming to enhance convective and diffusive sodium removal during dialysis (18).

Gentle and gradual reduction in post-dialysis weight until patients reach an “ideal” dry-weight with minimal signs and symptoms of either hypervolemia or hypovolemia is the standard-of-care of volume management among hypertensive hemodialysis patients (19). In the Dry-weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial (20), an average reduction in post-dialysis weight of 0.9 kg during 4 weeks was accompanied by a parallel reduction of 6.9/3.1 mmHg in 44-hour interdialytic ambulatory BP. Notably, this BP-lowering effect was evident in patients without clinically overt volume overload already treated with ~2.7 antihypertensive medications (20), indicating that uncontrolled interdialytic hypertension should be considered as a sign of sub-clinical volume expansion. Ensuring the adequate duration of the delivered dialysis enhances intradialytic sodium and

volume withdrawal, minimizes the risks of high ultrafiltration rates and facilitates the challenging process of dry-weight probing (21).

Initiation or intensification of antihypertensive therapy without adequate management of sodium and volume is an ineffective approach to control BP (16;22). Clinical studies have associated excessive antihypertensive drug use with higher prevalence of uncontrolled hypertension (2). This paradoxical association may be explained by the fact that intensified antihypertensive therapy may be a barrier against dry-weight achievement. The above non-pharmacologic treatment considerations are extensively discussed by other articles in this issue of Seminars in Dialysis.

PHARMACOLOGICAL MANAGEMENT OF HYPERTENSION

BP-lowering and clinical outcomes

In a meta-analysis of 8 randomized trials (incorporating data from 1,679 patients), a significant reduction of 4.5/2.3 mmHg in BP was noted in patients actively-treated with antihypertensive drugs relative to those assigned to control therapy (13). BP-lowering was associated with reduced risk for cardiovascular events [Relative Risk (RR): 0.71; 95% Confidence Interval (CI): 0.55-0.92] and all-cause mortality (RR: 0.80; 95% CI: 0.66-0.96) (13). Another meta-analysis of 5 randomized trials (incorporating data from 1,202 patients) showed that compared with placebo or no treatment, BP-lowering with antihypertensive drugs was associated with a 31% reduced risk for cardiovascular morbidity [Hazard Ratio (HR): 0.69; 95% CI: 0.56-0.84] (12). Cardiovascular risk reduction was greater when participants in individual trials were hypertensives (HR: 0.49; 95% CI: 0.35-0.67) (12). This evidence supports our belief that BP-lowering among patients on hemodialysis is not harmful; in contrast, antihypertensive therapy improves cardiovascular outcomes.

The feasibility and safety of intensive BP-lowering was tested in the Blood Pressure In Dialysis (BID) trial (14), in which 126 hypertensive hemodialysis patients were randomized to a lower predialysis systolic BP target of 110-140 mmHg (intensive arm) versus a higher predialysis systolic BP target of 155-165 mmHg (standard arm). Between baseline and month 4, systolic BP fell from 160 to 145 mmHg in the intensive arm, but remained unchanged in the standard arm. During months 4-12, the average difference in predialysis systolic BP levels between the 2 arms was 12.9 mmHg (14). Although the BID trial was under-powered to assess differences in clinical outcomes, the incidence of major adverse cardiovascular events, hospitalizations and vascular access thrombosis was not different between the intensive and standard arms (14). A phase 3 trial comparing different home BP targets is now warranted to elucidate whether intensive BP-lowering improves survival and clinical outcomes among patients on hemodialysis.

Choice of the appropriate antihypertensive regimen

With the exception of diuretics, all major antihypertensive drug classes are useful for pharmacological management of hypertension (15). Loop diuretics are reported to enhance urine output and limit IDWG among patients with preserved residual diuresis (23). Whether

this approach is translated into a benefit in BP control or in long-term outcomes remains unknown and needs to be tested in randomized trials.

In the following sub-sections, we discuss the cardiovascular safety and efficacy of major antihypertensive drug categories among patients on hemodialysis, focusing on clinical-trial evidence.

ACEIs/ARBs or their combination: Contrary to the established cardioprotective action of agents blocking the renin-angiotensin-system (RAS) in the general population, angiotensin-converting-enzyme-inhibitors (ACEIs) or angiotensin-receptor-blockers (ARBs) were not consistently associated with improvement in clinical outcomes among those on hemodialysis. In the Fosinopril in Dialysis (FOSIDIAL) trial (24), 397 hemodialysis patients with left ventricular hypertrophy (LVH) - not necessarily hypertensives - were randomized to fosinopril (5-20 mg/day) or placebo for 24 months. Fosinopril was not superior to placebo in reducing the risk of fatal and non-fatal cardiovascular events (RR: 0.93; 95% CI: 0.68-1.26), despite the significant BP-lowering effect of active therapy in the subgroup of hypertensives (24).

In contrast, a small Japanese study comparing the ARB candesartan (4-8 mg/day) versus no treatment in 80 hemodialysis patients showed that the incidence of fatal and non-fatal cardiovascular events was lower in actively-treated participants versus no treatment (25). Another Japanese trial compared the effect of an ARB-based therapy (valsartan, candesartan and losartan) versus a therapy without ACEIs/ARB in 366 hypertensive hemodialysis patients (26). Over a follow-up of 36 months, the ARB-based regimen lowered by 49% the risk for cardiovascular events and all-cause mortality (HR: 0.51; 95% CI: 0.33-0.79) (26).

This favorable effect of ARBs was not confirmed in a the Olmesartan Clinical Trial in Okinawa Patients Under Okinawa Dialysis Study (OCTOPUS) trial (27), in which 469 Japanese hemodialysis patients with hypertension were randomized to olmesartan (10-40 mg/day) or therapy without ACEIs/ARBs for 42 months. ARB-based antihypertensive therapy had no effect on the primary endpoint, defined as the composite of all-cause death, non-fatal stroke, non-fatal myocardial infarction (MI) and coronary revascularization (HR: 1.00; 95% CI: 0.71-1.40) (27).

The absence of benefit with RAS-blockers is further supported by the Saving Residual Renal Function among Hemodialysis Patients Receiving Irbesartan Study (SARIF) (28). This trial showed that among 82 incident hemodialysis patients, 12-month-long therapy with the ARB irbesartan was not superior to placebo in causing regression of target-organ damage, as assessed by measuring left ventricular mass index (LVMI) and aortic pulse wave velocity (PWV) (28).

The effect of combined therapy with an ACEI and an ARB on clinical outcomes was investigated in a double-blind trial, in which 332 Italian hemodialysis patients with congestive heart failure (CHF) and left ventricular ejection fraction (LVEF) <40% were randomized to telmisartan (80 mg/day) or placebo added to standard therapy with an ACEI for 35.5 months (29). Compared with monotherapy, dual RAS-blockade reduced by 49% the

risk of all-cause mortality (HR: 0.51; 95% CI: 0.32-0.82), by 58% the risk of cardiovascular mortality (HR: 0.42; 95% CI: 0.38-0.61) and by 62% the risk of hospitalization due to worsening CHF (HR: 0.38; 95% CI: 0.19-0.51) (29). This benefit of dual RAS-blockade may be not generalizable to the overall hemodialysis population, since patients participating in this trial were intensively treated with 4 dialysis session/week due to severe CHF. Additional randomized trials are needed to test the tolerability of dual RAS-blockade in those receiving conventional thrice-weekly hemodialysis, owing the high risk of hyperkalemia (30), particularly during the 3-day interdialytic interval (31).

β-blockers: In contrast to the general population where β-blockers are not recommended as first-line antihypertensive therapy by several international guidelines (32), emerging clinical-trial evidence support the notion that among those on hemodialysis, β-blockers exert potent BP-lowering effects and reduce cardiovascular morbidity and mortality. Cice et al. (33) randomized 114 hemodialysis patients with dilated cardiomyopathy to carvedilol (titrated up to 25 mg twice daily) or placebo for 24 months. Compared with placebo, carvedilol lowered by 56% the risk of all-cause hospital admission (HR: 0.44; 95% CI: 0.25-0.77) and by 49% the risk of all-cause death (HR: 0.51; 95% CI: 0.32-0.82) (33).

The efficacy of β-blockade is supported by the HDPAL trial (34). In this trial, 200 hemodialysis patients with hypertension and echocardiographically documented LVH were randomized to atenolol or lisinopril, each administered thrice-weekly after dialysis. Contrary to the primary hypothesis that an ACEI-based regimen would be superior to atenolol in causing regression of LVH, HDPAL trial showed no between-drug difference in the change of LVMI during the 12-month-long follow-up (34). Although no significant difference in change of 44-hour ambulatory BP was noted between drugs, HDPAL participants assigned to the lisinopril-based regimen had consistently higher monthly monitored home BP, required greater intensification of background antihypertensive therapy and had greater need for reduction in postdialysis weight; accordingly, atenolol exerted a more potent BP-lowering action. The superiority of atenolol is further supported by the premature termination of the HDPAL trial due to excess risk for serious cardiovascular adverse events in the lisinopril group (34). Incidence of the combined safety outcome of MI, stroke, hospitalization for worsening CHF and cardiovascular death was 2.3-fold higher in lisinopril-treated participants [Incidence Rate Ratio (IRR): 2.29; 95% CI: 1.07-5.21] (34). In a secondary analysis of the HDPAL trial, atenolol was superior to lisinopril in reducing aortic PWV, an effect possibly mediated through the more potent BP-lowering action of atenolol (35).

The β-blocker to Lower Cardiovascular Dialysis Events (BLOCKADE) trial planned to recruit 150 hemodialysis patients with diabetes or cardiovascular disease from 11 dialysis centers in Australia and New Zeeland aiming to compare the cardioprotective properties of carvedilol versus placebo (36). In contrast to the HDPAL trial that successfully recruited 200 hemodialysis patients (34), the BLOCKADE trial failed to explore its original research hypothesis due to low recruitment rate. Of the 354 patients eligible in the trial, only 72 entered the run-in phase and only 49 participants (68%, 95% CI: 57%−79%) tolerated low-dose carvedilol therapy (6.25 mg twice daily) during the 6-week-long run-in (36). Whether

this low recruitment rate is attributable to strict inclusion/exclusion criteria, reluctance of physicians to wash-out background therapy with β-blockers or to other reasons is unknown.

Calcium-channel-blockers: In a double-blind fashion, 251 hypertensive hemodialysis patients were randomized to the calcium-channel-blocker (CCB) amlodipine (10 mg/day) or placebo for a median follow-up of 19 months (37). Compared with placebo, amlodipine was associated with a trend towards reduction in the risk of all-cause mortality (HR: 0.65; 95% CI: 0.34-1.23) (37). However, amlodipine significantly lowered by 47% the occurrence of the secondary endpoint, defined as a composite of all-cause death, nonfatal stroke, MI, coronary revascularization, and angioplasty for peripheral vascular disease (HR: 0.53; 95% CI: 0.31-0.93) (37). Other studies showed that CCBs exert beneficial effects on a number of surrogate endpoints such as LVMI, carotid intima-media thickness and oxidative stress (38;39).

***M*ineralocorticoid-receptor-antagonists:** Whether mineralocorticoid-receptor-antagonists (MRAs) have a role in pharmacotherapy of hypertension among hemodialysis patients still remains unclear (40). A beneficial effect of MRAs is supported by the Dialysis Outcomes Heart Failure Aldactone Study (DOHAS) (41), in which 309 Japanese oligo-anuric hemodialysis patients were randomized to add-on therapy with spironolactone (25 mg/day) or nothing for a 3-year-long period. Spironolactone lowered by 60% the risk for hospitalization or death from cardiovascular and cerebrovascular events (HR: 0.40; 95% CI: 0.20-0.81) (41). A survival benefit with MRAs is also supported by another randomized trial enrolling 253 long-term dialysis patients without overt CHF. Over a 2-year-long follow-up, spironolactone (25 mg/day) was associated with 58% reduction in the risk of death from cardio-cerebrovascular event, cardiac arrest or sudden death (HR: 0.42; 95% CI: 0.26-0.78) (42).

A meta-analysis of 9 randomized trials showed that MRA therapy was associated with 60% reduction in the risk of all-cause mortality relative to control therapy (RR: 0.40; 95% CI: 0.23-0.69), but MRA use significantly increased the risk of hyperkalemia (RR: 3.1; 95% CI: 1.2-7.7) (43). The hyperkalemia risk associated with MRAs was evaluated in a non-inferiority trial, in which 144 hemodialysis patients were randomized to eplerenone (50 mg/day) or placebo for 13 weeks. Compared with placebo, hyperkalemia (defined as serum potassium >6.5 mEq/L) was 4.5 times higher in eplerenone-treated participants (RR: 4.5; 95% CI: 1.0-20.2) (44). The safety and efficacy of MRAs among patients on hemodialysis is under investigation in the ongoing ALCHEMIST trial (45). In the mean-time, the wide use of MRAs among hemodialysis patients is not evidence-based.

Summary of clinical-trial evidence: Choice of the appropriate antihypertensive regimen among those on hemodialysis should not rely on extrapolation of evidence derived from the general population or those with earlier stages of chronic kidney disease (15;46;47). To wit, trials that evaluated the efficacy of ACEIs/ARBs suggest that their use as first-line antihypertensive therapy in hemodialysis patients is not supported by strong evidence of a cardiovascular benefit (24;27;28). By contrast, the BP-lowering efficacy of atenolol in the HDPAL and its premature termination due to excess risk for serious cardiovascular adverse events in lisinopril-treated participants support the use of β-blockers

as first therapeutic choice (34). However, this approach requires stronger supportive evidence from a phase 3 trial. The use of CCBs as add-on or combination therapy is supported by their potent and long-lasting BP-lowering efficacy that enables their once daily administration (15;46;47). In the absence of "hard" clinical-trial evidence to elucidate the benefits and risks of MRAs, the wide use of spironolactone or eplerenone among hemodialysis patients should be avoided (40). Individualization of antihypertensive therapy on the basis of clinical characteristics, co-morbid conditions and the overall risk profile of each patient should be the standard-of-care.

Dialyzability of antihypertensive drugs: The dialyzability of antihypertensive drugs is another factor that should be taken into consideration (15;46;47). With the exception of the non-dialyzable fosinopril, most of the other ACEIs are removed during dialysis. The dialyzability of β-blockers depends on their molecular structure; hydrophilic β-blockers (such as atenolol) are highly dialyzable. In contrast, ARBs and CCBs are generally not dialyzable and no supplemental doses are required when these agents are administered before dialysis (15;46;47). A useful maneuver is to administer agents with high dialyzability in a thrice-weekly regimen immediately post-dialysis. This notion is strongly supported by the HDPAL trial (34). Administration of atenolol and lisinopril 3 times per week after dialysis culminated in sustained BP reductions over the 12-month-long follow-up of HDPAL (34).

CONCLUSION

Management of hypertension among patients on hemodialysis is challenging. Non-pharmacological strategies including dietary sodium restriction, individualized prescription of dialysate sodium, optimized assessment and management of dry-weight play a pivotal role and should be first-line approaches. Initiation and intensification of antihypertensive drug therapy is proven to be beneficial only after the adequate management of volume overload. Once again, antihypertensive therapy among those on hemodialysis should be individualized and treatment considerations may differ from those used in the general hypertensive population. Clinical-trial evidence supports the use of β-blockers – particularly atenolol thrice-weekly after dialysis - as first choice agents in pharmacotherapy of hypertension in hemodialysis. Long-acting CCBs followed by ACEIs/ARBs are our next therapeutic choices, in relation to the clinical characteristics and risk profile of each patient. Randomized trials to elucidate the optimal BP targets and the comparative effectiveness of non-pharmacological and pharmacological interventions are clearly needed in order to move a step forward and improve the management of hypertension in those on hemodialysis.

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